Justification

National Center for Research Resources

Authorizing Legislation:	Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
103	$674,569,000	112	$817,253,000	120	$974,038,000	8	$156,785,000

INTRODUCTION

This document provides justification for the Fiscal Year 2002 activities of the National Center for Research Resources (NCRR), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

With the human genome essentially sequenced, along with the genomes of dozens of other organisms, biomedical science is entering a new age. In this post-genome sequencing era, researchers are grappling with enormous datasets that hold critical information about the body's tiniest components—the genes and proteins that underlie human health and disease. The challenge researchers now face is piecing together or integrating these bits of information into a more complete and complex picture—one that provides important clues to human biology and disease.

Determining how thousands of genes and proteins function together in the cell is a puzzle of staggering proportions. But it is a problem worth tackling, for the sum of these research efforts will be much greater than its parts. Each step toward a solution holds enormous promise for improving human health. But solving the puzzles of the genome will depend on scientific access to appropriate tools and research infrastructure.

The NCRR ensures that essential tools and research resources are readily available to the scientific community. NCRR has a trans-NIH mandate to provide the critical research infrastructure that enables all lines of biomedical inquiry, from the molecular level to whole organisms. By supporting biomedical technology resources and shared instrumentation, NCRR enables access to a variety of advanced technologies, including high-performance computers, microarray technologies, and sophisticated imaging systems that can reveal how mutations affect the development and function of the brain or other organs. NCRR's comparative medicine

resources—including the national network of Regional Primate Research Centers—enhance access to normal and specialized animal models that are critical to discovering the functions of genes and proteins. And the 78 NCRR-supported General Clinical Research Centers, located at medical centers nationwide, provide resources for assuring that the knowledge gained from basic research will benefit patients. NCRR also serves to broaden the scope of biomedical research by enhancing research infrastructure and career development opportunities at minority and other institutions through the Research Centers in Minority Institutions program, Research Facilities Improvement program, and the Institutional Development Award program.

All of these NCRR-supported research resources are shared by thousands of investigators. That cost-effective approach maximizes the impact of scarce or expensive research resources and scientific expertise. NCRR-supported resources are utilized each year by more than 20,000 investigators, who receive more than $3.6 billion in competitive grants from the other NIH components. To enhance access to costly technologies, NCRR also forms partnerships with other funding agencies, such as the Department of Energy and the National Science Foundation (NSF). These two agencies operate the nation's synchrotron facilities, which produce brilliant x-ray beams that can determine the structures of biological molecules at high resolution. NCRR is working with these agencies to boost biomedical investigations at synchrotron resources. In addition, NCRR has teamed up with the NSF-supported San Diego Supercomputer Center, one of two National Partnerships for Advanced Computational Infrastructure, to facilitate biomedical investigators' access to web-based computational biology tools to analyze gene expression arrays, determine gene function and regulation, and address many other biologic problems.

Through close and constant contact with the biomedical research community, NCRR strives to anticipate infrastructure needs that provide ready access to critical research tools. In the post-genomic era, these tools will be essential to piecing together functional information about thousands of genes and proteins, and integrating that information to gain new understanding of the complexities of the human body.

Story of Discovery: Simian Immunodeficiency Virus Models the Human AIDS Virus

More than 20 years ago—as concerns about a mysterious and deadly new disease known as acquired immunodeficiency syndrome (AIDS) began to sweep the nation—scientists at the California Regional Primate Research Center (RPRC) were puzzling over a new outbreak of infections that were decimating their monkey colonies. Inexplicably, dozens of animals became dangerously thin and weak, and many developed malignant tumors, severe herpesvirus or bacterial infections, anemia, or inflammation of brain tissues. Most affected animals were dead in a matter of months. Meanwhile, on the other side of the country, researchers at the New England RPRC near Boston noticed a similarly disturbing trend among their macaque monkeys. As investigators launched a search for the disease-causing agent, they little suspected the enormous impact their efforts would later have on understanding AIDS virus infections in humans and developing methods for its treatment, control, and prevention.

The more researchers learned about the monkey syndrome, the more obvious it became that the human and simian disorders were strikingly similar. Both diseases were marked by a weakened immune system that laid the body vulnerable to a variety of infections that normally did not cause disease. Scientists on both coasts began to suspect that studies of this monkey immunodeficiency disorder, or simian AIDS, could provide otherwise-unobtainable insights into the progression of human AIDS.

Back in 1980 no one knew what caused AIDS—suspects ranged from a variety of viruses to a recreational drug known as poppers. Without knowing the causative agent, it was impossible to study or diagnose the earliest stages of human infection. A critical lead came in 1983, when two teams of scientists independently isolated a new human retrovirus—with a genome consisting of RNA rather than DNA—from the tissues of AIDS patients. Skeptics questioned whether this virus, now known as the human immunodeficiency virus (HIV), could produce the severe immunodeficiency characteristic of AIDS. Only two other retroviruses were known to infect humans, and both of these caused cancer. Crucial support for a retroviral basis of AIDS in primates came when RPRC investigators isolated and identified a new virus, which they dubbed simian retrovirus-1 (SRV-1), from the tissues of AIDS-affected animals in 1984. When the isolated virus was injected into healthy monkeys, the animals developed an AIDS-like disorder within 2 to 4 weeks. Studies of simian AIDS offered the first opportunity to track the immune system's initial response to this highly contagious retrovirus.

Although SRV-1 triggers an AIDS-like disease, researchers were disappointed to learn that the simian virus was unexpectedly different—structurally and genetically—from HIV. Scientists at the New England RPRC decided to systematically search for HIV-like viruses (lentiviruses) in their primate colonies. They eventually isolated the virus now known as the simian immunodeficiency virus (SIV) from several species. As the closest known relative of HIV, SIV not only looks similar to the human virus under the microscope, but also has similar genes, biological properties, and effects on the immune system. Like its human counterpart, the simian virus particularly infects and destroys white blood cells known as T-helper (or CD4) cells. Because these cells are required for the body to mount an effective immune response against disease-causing agents, their destruction explains the profound immunodeficiency seen in humans and monkeys with AIDS.

SIV infection of macaques is now widely considered the best animal model for human AIDS and is used by hundreds of AIDS researchers worldwide. In many cases, SIV infection progresses to AIDS rapidly—in a matter of months rather than the decade typically seen in HIV-infected humans—which makes the animal model suitable for timely investigation of the disease process. The model has proven especially useful for evaluating potential AIDS vaccines. Monkey studies allow scientists to challenge vaccinated animals with potent strains of virus to determine if the vaccine is protective.

Some SIV vaccines completely protect animals from even the most deadly variants of SIV. These vaccines are made of live, but weakened (or attenuated) strains of SIV in which one or more viral genes are deleted. Vaccinated animals have remained virus-free and healthy for years after complete viral challenge. Live attenuated AIDS vaccines may be deemed too risky for human use, since the weakened virus may still be capable of causing disease in some recipients. However, the monkey studies offer proof of principle that it is possible to develop an AIDS vaccine that can prevent infection. Researchers are now scrutinizing the immune responses of vaccinated monkeys to identify the factors that keep SIV infection at bay.

Many experiments suggest that antibodies alone are incapable of thwarting an SIV attack, and that protection against the AIDS virus will also depend on activation of white blood cells known as killer (or cytotoxic) T-cells. These cells take advantage of the fact that SIV- and HIV-infected CD4 cells display several viral proteins on their surfaces, and so can be easily identified and destroyed. In fact, RPRC-supported investigations have shown that a powerful army of killer T-cells can nearly eliminate all traces of SIV from the body in the first weeks of infection by homing in on a viral protein known as Tat. Although Tat is displayed on all SIV- and HIV-infected CD4 cells, a few viruses have mutant versions of Tat, which allows them to escape the killer T-cell assault. Eventually, these mutant viruses are able to repopulate the animal's bloodstream and cause full-blown infection. Identification of specific Tat mutations may assist the design of effective AIDS vaccines that stimulate a broader killer T-cell response. Scientists have also identified portions of additional viral proteins that are displayed on infected cells and might be used to further enhance potential AIDS vaccines.

Studies of SIV in macaques have also shed light on the factors that affect transmission of the AIDS virus from one individual to another. In humans, HIV is most often transmitted when mucosal surfaces are exposed to infected fluids, usually during sex or birth. Monkey studies allowed scientists to identify the mucosal cells in females that are initially infected during heterosexual transmission of the virus. The SIV model also confirmed that the virus

could be transmitted to newborns that swallow amniotic fluids or breast milk from infected mothers. These discoveries open new opportunities for blocking HIV transmission with drugs, vaccines, or other precautions.

The SIV model also enhances understanding of the brain and nerve damage that often accompanies AIDS. Although HIV-infected patients are now living longer thanks to improved therapies, some clinicians fear that these longer lives may be marred by AIDS-associated dementia. SIV experiments suggest that infection of blood cells known as monocytes and macrophages play a critical role in transporting the virus across the blood-brain barrier, and recent investigations of HIV infection in humans support these conclusions. Therapies that target these cells may therefore help limit the risk of developing AIDS dementia.

The sudden appearance and rapid spread of human AIDS illustrate how quickly a virus can infect a new species and cause a global pandemic. Ongoing studies are piecing together the factors that enabled SIV in nonhuman primates to jump to human hosts and cause such a devastating disease. One puzzling paradox is that many species of monkeys and apes are infected in the wild with their own distinct variants of SIV but show no disease symptoms and apparently do not mount immune responses against the viruses. This unique tolerance is not yet fully understood but might help scientists understand the mechanisms of HIV pathogenicity—and how to protect against it. Such investigations may also offer clues to preventing or reducing cross-species transmission of other emerging viruses, such as the West Nile virus, which naturally infects birds but has recently killed several people in the United States.

The knowledge gained from studies of SIV demonstrates the importance of studying diseases that arise spontaneously in animals. Because scientists were alert to changes in the health of their nonhuman primate colonies, and because they had access to unique scientific resources and expertise at the RPRCs, they were able to develop an animal model that continues to provide critical insights into the understanding and treatment of human AIDS.

Science Advances

Genomics and Genetic Medicine

Global Screening of Protein Interactions

The recent deciphering of the human genome will gain medical significance only when scientists can determine how these genes and their protein products orchestrate the complex functions within each cell. Understanding this intricate web of protein interactions requires new large-scale or systems approaches and new research tools. In collaboration with a biotechnology company, researchers at an NCRR-supported yeast genetics resource have developed an automated system for genome-wide screening of thousands of protein interactions that might occur within a cell. This new technology was initially tested in baker's yeast (*Saccharomyces cerevisiae*), and serves as a model organism for understanding the human genome and its modulation of normal biology and disease. Using a technique known as the two-hybrid assay and high-throughput technology to identify novel protein interactions, the researchers detected nearly 1,000 putative protein-protein associations, many of which involved unknown yeast proteins that can now be studied in new contexts. This information will provide valuable insights into the relationships between specific human genes and complex diseases such as metabolic disorders and cancer.

A Genetic Linkage Map of the Baboon Genome
NCRR-supported scientists at the Southwest Regional Primate Research Center and their collaborators have developed a genetic linkage map for the baboon. The linkage map, which identifies the sites of various genes or gene functions along the baboon chromosomes, is the first reported for any nonhuman primate species. Because of its remarkable similarities to the human linkage map, the baboon linkage map opens new opportunities for studying the functions of genes that play important roles in human health and disease. The discovery also marks a first step toward mapping the genomes of other nonhuman primates, which will enhance comparative studies of genes and gene functions.

Mutations Within a Skeletal Muscle Gene Cause Muscle Disease
Myotonia congenita is a genetic disease associated with abnormalities in the skeletal muscle chloride channel which results in altered control of muscle movement. The disease is characterized by intermittent and progressive weakness. To date, more than 35 mutations, or variants, of the chloride channel gene (CLCN1) have been identified. To characterize the physiological effects of five of these variants, investigators at an NCRR-supported General Clinical Research Center isolated the mutant genes and introduced them into cultured cells. Studies of these cells documented alterations in chloride ion passage through each of these uniquely modified channels and confirmed that each of the modified channels represents a different form of the disease. Researchers can now design drugs that are specific for each disease—or chloride channel—variant.

University of Hawaii Identifies First Gene Mutations in Elastic Tissue Disease
Pseudoxanthoma elasticum (PXE), a relatively rare disorder that occurs in about 1 in 100,000 individuals, according to the National Association for Pseudoxanthoma Elasticum, can have devastating consequences. In PXE, elastin fibers between cells of the skin, retina, and arteries become calcified and lose their resilience. Skin can show premature aging, bleeding in the retina can cause blindness, and premature arteriosclerosis can necessitate heart bypass surgery in patients still in their twenties. By comparing DNA from unrelated PXE patients and normal individuals, an international research team headed by NCRR-supported University of Hawaii investigators identified the disease-causing gene, which produces a transport protein that shuttles proteins across cell membranes. The PXE gene has been associated with drug resistance that results from the failure of the drug to cross the cell membrane. Studies of the PXE gene and its protein product may contribute to a better understanding of how drugs and other compounds enter cells.

New Vector Enhances Gene Transfer
The blood-forming, or hematopoietic, stem cells found in bone marrow are attractive targets for gene transfer. By inserting new genes into these cells, which give rise to many different types of blood cells, gene researchers hope to establish a long-term source of genetically altered cells in the bone marrow. But once administered to living organisms, hematopoietic stem cells (HSCs) and their cellular offspring often rapidly lose their capacity to express therapeutic genes. This problem might be solved with a more effective "vehicle" for transferring foreign genes to the HSCs. Investigators at the NCRR-supported New England Regional Primate Research Center observed that a genetically modified monkey virus called SV40 can effectively deliver foreign genes to both human and monkey HSCs in culture. When transplanted into mice, the HSCs

continued to express their foreign (or new) genes for at least three months, which is a remarkable achievement. Such a vector, if proven safe and effective, could lead to the treatment and potential cure of several genetic and infectious diseases.

Bioengineering, Bioimaging, and Bioinformatics

Identifying the Functions of Proteins

Determining sequence homology is often a useful starting point for determining gene function. However, a third to one half of the identified genes are unique, meaning they have no homology, or sequence similarity, to previously identified genes. For genes with no sequence homology, it may be necessary to develop a new technology to identify their function. Scientists at an NCRR-supported biomedical technology resource used a combination of conventional separation methods, mass spectrometry, conventional light microscopy, and electron microscopy to identify 40 unique proteins that formed a pore between the cell nucleus and the cytoplasm of yeast cells. This pore allows large molecules to enter and exit the cell nucleus. These studies offer clues to similar functions in human cells and provide targets for development of drugs for diseases involving nuclear transport defects.

Imaging a Molecular Switch

To develop drugs that interact specifically with particular molecules, researchers often must determine the detailed molecular structures by x-ray crystallography. Using the intensely penetrating x-rays produced at the NCRR-supported MacCHESS synchrotron facility at Cornell University, scientists solved the three-dimensional structure of a protein known as Cdc42 while it was bound to another protein, GDI (guanine nucleotide dissociation inhibitor), that regulates the biological activities of Cdc42 like an on-off switch. The structure revealed significant details of the interactions between the two molecules. Cdc42 belongs to a family of proteins that influence gene expression and cell growth that may lead to cancer. Understanding the detailed functions of these proteins may help scientists develop targeted drugs that block tumor growth.

Visualization of the Herpesvirus Capsid

Human herpesviruses are large and structurally complex viruses that infect more than half the population of the United States and cause a variety of medical problems ranging from cold sores to blindness to cancer. When a herpesvirus invades a cell, it disassembles and releases a large protein structure, called a capsid, that encloses the viral genetic material. The capsid then delivers its DNA into the nucleus of the cell, where the viral DNA is incorporated into the cellular DNA and causes the host cell to create more viruses. Using electron cryomicroscopy at the NCRR-supported National Center for Macromolecular Imaging (NCMI), scientists uncovered the three-dimensional structure of the 20-sided polyhedron-shaped capsid of herpes simplex virus type 1 (HSV-1). NCMI researchers have developed software to visualize and animate the 3-D image of this extremely complex virus using computer graphics. Knowledge of the herpesvirus structure may facilitate development of more effective antiviral therapies.

Shining a Light Through Brain Tissue

Scientists at the Stanford University General Clinical Research Center safely and noninvasively imaged changes in brain oxygen levels in adults and critically ill newborns who wore a thin, flexible headband that contains optical fibers. The headband fibers both emit and detect low-

intensity light that travels through brain tissues. Because that light is absorbed by blood, and because changes in blood oxygen levels alter the amount of absorption, the headband technology can pinpoint brain regions with fluctuating oxygen levels. Coupled with real-time computer analysis, the imaging technique holds promise as a bedside device for generating continuous, noninvasive brain images that enable diagnosis or monitoring of disease progression.

Biology of the Nervous System: Development and Disorders

MRI Reveals Changes in Brain Structure Associated with Multiple Sclerosis

Multiple sclerosis (MS), an inflammatory disease of the central nervous system, occurs in two different forms: relapsing-remitting and progressive. In many patients, the progressive form of the disease occurs after a relapsing-remitting stage, but in some patients the disease is progressive from onset. Improved tools are needed to identify different forms of the disease and accurately and efficiently measure disease status. Researchers at Brigham and Women's Hospital General Clinical Research Center used magnetic resonance imaging (MRI) to observe lesions in patients with different forms of MS and discovered differences between patients with relapsing-remitting MS and those with progressive MS. The MRI images clearly correlated with the traditional clinical scales used to evaluate the progression of multiple sclerosis, thus showing that MRI can provide objective measures of patient responses to experimental treatments.

Parkinson's Disease Treatment in Nonhuman Primate Model

Parkinson's disease (PD), which affects primarily the elderly, can be defined by stages. At the onset of clinical symptoms, tremor, limb stiffness, slowness of movement, and gait disturbances appear but do not interfere with daily life. Advanced stages are characterized by increasing disability that necessitates living assistance. At present, drug therapies are largely designed to replace the essential brain chemical dopamine, which is produced in insufficient quantities in PD patients. NCRR-supported scientists have found that D1 dopamine receptor agonists appear to be more promising for treating advanced, rather than mild, stages of PD. Objective assessments of drug efficacy in an animal model of both early and late stages of PD will expedite the development of new, effective therapeutics.

Imaging Technique Reveals Changes in Brain Structure

Human development, as well as degenerative disease processes, is known to affect the volume of brain substructures. But detecting, tracking, and quantifying these structural changes have proven difficult, in part because observations must be made throughout the brain and must be made at different times. Researchers at the NCRR-supported Laboratory of Neuro Imaging at the University of California-Los Angeles now have created detailed three-dimensional images that map growth patterns in the developing human brain over time. The researchers discovered that different parts of the brain grow at markedly different rates during child development. Between the ages of three and six, growth rates peaked in an area of the brain responsible for mental vigilance and planning of new actions. Older children displayed fastest growth in a region of the brain related to spatial association and language function. The researchers also found that the areas of the brain that grow fastest in children also degenerate fastest during the early stages of Alzheimer's disease. The sensitivity of the new experimental approach may help in tracking the effects of various treatments for Alzheimer's disease and other brain disorders.

New Preventive Strategies Against Disease

Advanced Imaging Technique Helps Predict Risk for Alzheimer's Disease
According to the National Institute on Aging, an estimated 4 million Americans now suffer from Alzheimer's disease (AD), while countless others are impaired by related dementia disorders. Investigators at the NCRR-supported Neuroimaging Analysis Center have used magnetic resonance imaging (MRI) to determine whether persons in the preclinical phase of AD could be accurately identified before they developed clinically diagnosed dementia. The MRI scans of various brain regions showed significant differences between normal individuals and those who later developed AD and predicted which patients with memory impairment would develop AD.

A second study conducted at the NCRR-supported Center for Advanced Magnetic Resonance Technology at Stanford University concluded that magnetic resonance spectroscopy may be a suitable noninvasive tool for monitoring disease progression in patients with AD. Serial measurements of the brain chemical N-acetyl aspartate, a marker for living brain cells, showed significant reductions in patients with AD over a 1-year period. This work is particularly important because it may enhance evaluation of the many new drugs currently being developed to treat AD.

Fingerprinting Bacteria
Identification of pathogenic bacteria is important for diagnosing disease and assessing the safety of food and water. Rapid identification of bacteria would allow physicians to administer early, specific therapies to their patients. Scientists at the NCRR Flow Cytometry Resource Center, Los Alamos National Laboratory, have developed a new technique for bacterial identification that lowers the cost and speeds the analysis of DNA samples extracted from bacteria. The technique provides greater precision and a wider range of applications than current methods. DNA extracted from as few as 1,000 bacteria are treated with specific enzymes that cleave the DNA into fragments, the lengths of which are unique to particular bacteria. This mixture of DNA fragments is passed through a flow cytometer, and within 10 minutes the DNA "fingerprint" of the organism is known. Using this method, it is possible to distinguish between harmless strains of *E. coli* and the toxic strains that cause food poisoning. The scientists are designing an inexpensive portable version of their laboratory equipment to enable its use in hospital settings.

Mechanisms of Chromosome Missegregation in Cancer Cells
When a normal, healthy cell begins to divide, its chromosomes line up along the center of a structure called a spindle. As the cell divides, thread-like structures called microtubules guide the chromosomes to form two new cells. In cancer cells this delicate process becomes faulty, resulting in a large number of chromosome deletions and structural abnormalities. Such abnormalities are among key features used by pathologists to diagnose cancer. By using fluorescence microscopy to study oral cancer cells, researchers at the University of Pittsburgh supported by an NCRR Shared Instrumentation Grant have visualized the mechanisms by which chromosomes are distributed unevenly during cancer cell division. This is the first study to show why cancer cells contain too few or too many chromosomes. Using this information, investigators may be able to screen individuals at risk for cancer, as well as develop and apply better prevention and treatment strategies.

Elevated Autoantibody Levels in Coronary Artery Disease
Autoantibodies are antibodies produced by the body's immune system against specific parts of its own body. Autoantibodies against actin and myosin (proteins that may be exposed in damaged heart muscle) and autoantibodies against troponin (a complex protein involved with heart muscle contraction) were found to be elevated in patients who had had a recent acute heart attack. Investigators at the Mt. Sinai School of Medicine General Clinical Research Center found that in 33 patients, followed from the time of the acute heart attack to 3 months following it, all three types of autoantibodies were elevated. In patients with higher levels of these three autoantibodies, there was a higher risk of a later myocardial infarct or heart attack. Alternatively, the data also suggest that elevated levels of these autoantibodies may represent markers of earlier or ongoing heart tissue damage and can prompt implementation of preventive measures.

Anti-insulin Autoantibodies in Young Children Predict Diabetes
Type 1 diabetes strikes approximately 1 in 600 children, according to the American Diabetes Association, and is one of the most frequent chronic, life-threatening illnesses of children. Scientists have long known that development of anti-insulin autoantibodies can precede the clinical development of diabetes, but have not known how early these antibodies can be detected. To correlate development of disease with the presence of autoantibodies, researchers at the General Clinical Research Center at the University of Colorado Health Sciences Center in Denver developed a sensitive assay for anti-insulin autoantibodies. The investigators discovered that children developed anti-insulin autoantibodies in the first year of life, and four of five children expressing such antibodies progressed to diabetes before they were 3.5 years old. This new assay will permit public health screening for diabetes risk whenever effective preventive therapies become available.

New Approaches to Pathogenesis

Prenatal Androgen Exposure May Affect Insulin-Glucose Balance in Adulthood
Women with polycystic ovarian syndrome (PCOS) exhibit disorders characterized by hormone imbalances that may affect insulin and glucose metabolism. Scientists at the NCRR-supported Wisconsin Regional Primate Research Center used female rhesus monkeys to determine whether excessive exposure to male hormones (androgens) at different times during embryonic or fetal development would result in different types of insulin-glucose imbalance. Investigators found that monkeys exposed to the hormone testosterone early in gestation had impaired function of insulin-producing cells, but those exposed to the hormone late in gestation had difficulty utilizing insulin. It is possible that prenatal androgen exposure may induce impaired glucose metabolism in women with PCOS**.**

Maternal Immune Tolerance of the Fetus
Implantation of the fertilized egg into the uterine wall establishes the connection between the maternal blood supply and the mammalian embryo. Why the fetus is not rejected by the maternal immune system remains a critical question. Scientists at the NCRR-supported Wisconsin Regional Primate Research Center have identified a unique cell-surface molecule on the rhesus monkey placenta that shares many characteristics with a human placental molecule, HLA-G. The rhesus molecule—known as Mamu-AG—is expressed at the critical stages when the embryo-

placental complex is connecting to the maternal blood supply within the uterus. Mamu-AG expression is believed to prevent the maternal immune cells from rejecting the embryo. This animal model allows research to be conducted at the very earliest stages of pregnancy, a time in which the greatest number of spontaneous abortions occur in women.

Bacteriorhodopsin in its Native Environment
Membrane proteins are critical to the normal functioning of a cell, yet the details of their operations are poorly understood. Bacteriorhodopsin is a relatively small, simple membrane protein that can provide valuable insight into the principles governing membrane-protein function. By combining electron microscopic and crystallographic investigations, scientists at the NCRR-supported Resource for Macromolecular Modeling and Bioinformatics were able to build the first dynamic atomic-scale model of the entire cellular apparatus in its complete native environment. Analysis of such membrane proteins is expected to reveal a new world of channels, pumps, receptors, pores, and antigens important to disease and drug resistance.

Phospholamban Affects Contractility of the Heart
It is well known that heart muscle contractions increase in response to increased frequency of specific stimuli, but the underlying mechanism is not understood. In this study, phospholamban, a specific regulator of the calcium transport mechanism in the heart muscle, was evaluated for its involvement in cardiac contractility. Heart muscle tissue from mice with genetically deleted phospholamban failed to respond in the expected manner, while heart tissue from wild-type mice responded as predicted. The researchers supported by an NCRR mutant mouse resource concluded that they have identified phospholamban as a major determinant of the unknown contributors to the cardiac force-frequency relationship.

Receptor Causes Lethal Heart Disease and Abnormal Electrical Conduction
Dilated cardiomyopathy, a heart disease characterized by abnormal relaxation of the heart muscle and weakened pumping action, is a major cause of heart failure in the United States. While half of the cases are due to diseased heart arteries, the remainder, called idiopathic, have shown no discernable cause. Investigators associated with the General Clinical Research Center at San Francisco General Hospital now have shown a direct link between activation of a particular receptor (known as the Gi-coupled receptor) on the surface of heart cells and the development of most cases of the idiopathic form of dilated cardiomyopathy. Using genetically manipulated mice, the researchers showed that continuous activation of the Gi receptor gene led to cardiomyopathy, abnormal electrocardiograms, and death within 16 weeks. In contrast, suppression of Gi gene activation halted disease progression within 24 hours, and the electrocardiogram became normal. These studies point to a possible genetic mechanism for idiopathic cardiomyopathy and provide rational starting points for development of targeted patient therapies.

New Avenues for Development of Therapeutics

Mutant Mice Offer Clues to Mechanism of Heart Failure
Dilated cardiomyopathy, a condition marked by reduced contractility of heart muscle, is a major form of heart failure. The heart's pumping action at the cellular level is controlled in part by the cyclical movement of calcium ions into and out of a membrane sac—the sarcoplasmic

reticulum—in heart muscle cells. Because defective calcium cycling lies at the root of many heart disorders, deeper knowledge of these processes could lead to novel strategies for treating and preventing progressive dilated cardiomyopathy and other heart conditions. By studying transgenic mice at an NCRR-supported mutant mouse resource that have mutations in muscle-specific enzymes that affect calcium transport, investigators have demonstrated that the progressive defect in dilated cardiomyopathy is linked to these key molecules. Further studies of these important enzymes and processes may lead to development of new designer drugs or gene therapies to successfully prevent the sickness and death caused by dilated cardiomyopathy and end-stage heart failure.

Future Research Directions

Genomics and Genetic Medicine

Establish Integrative Biomedical Technology Centers. Using multiple complementary technologies, including techniques for protein purification, structural techniques, mass spectrometry, and DNA microarrays along with the necessary bioinformatics, multidisciplinary teams of investigators are examining progressively more complex biologic problems through an integrative or systems approach. That approach requires comprehensive resource centers equipped with several complementary technologies. Initial efforts will concentrate on proteomics. NCRR plans to support development of technologies to quantitate spatiotemporal differences in the levels of gene expression, assess post-translational modifications of proteins, and characterize intracellular protein-protein interactions in both healthy and diseased states.

Establish Regional Genotyping and Phenotyping Centers. Recently, investigators have announced that most of the human genome is sequenced and about 31,000 genes found. That information, combined with the identification of more than one million single nucleotide polymorphisms (SNPs) within the human genome will allow phenotyping/genotyping and pharmacogenetic studies to identify the genetic polymorphisms for many disease variants. Studies designed to examine the genetics of a complex disease require screening of very large numbers of patients. Massive quantities of data are of little practical use unless they are analyzed in conjunction with corresponding phenotypic information. For some current needs, investigators can design and obtain specific DNA chips within days for screening large numbers of patients. Technologies for high-throughput approaches to genotyping need to be developed as well. As wireless technology becomes available, bioinformatics tools will become more widely available and permit outreach to other sites. This effort will include workshops and training courses in bioinformatics for both new and established investigators. In addition, a web-based bioinformatics toolbox will be developed to address investigator needs.

Other phenotyping resources also need to be established for animal studies and include in vivo imaging, histopathology, biochemistry, and functional testing of sensory and motor neuronal functions and learning behavior. The data generated from genotyping and phenotyping will be included in a common database for animal-based research in order to reduce unnecessary duplication.

Develop the rhesus as a model of human disease. This multiyear effort includes development or adaptation of technologies and repositories to facilitate this activity, developed by the research community with major input by Regional Primate Research Centers-based investigators. This undertaking includes the sequencing of the rhesus genome, development of basic resources—BAC libraries, cDNA libraries, genetic linkage maps, radiation hybrid maps—along with other technologies for gene expression arrays. A complementary database along with state-of-the-art bioinformatics tools are essential for this undertaking. This model system will be invaluable in discerning how risk factors modulate gene function in polygenic disorders—diabetes mellitus and hypertension, for example. The rhesus macaque model is already an invaluable model to study brain function in degenerative brain disorders and possible therapies.

Develop Genetic Technologies for Nonhuman Primate Research. Powerful new genetic technologies have increased the expectation that nonhuman primate models will be "designed" specifically for AIDS vaccine and gene transfer research. A consortium of investigators will focus on genetic technology development to generate models for human monogenetic diseases, such as cystic fibrosis, in the nonhuman primate. Separately, the Regional Primate Research Centers will systematically search their colonies for new primate models with inborn errors of metabolism or other genetic defects developed spontaneously.

Establish Transgenic Rat Resources. A large volume of physiologic data exists for the rat. However, developing induced mutant strains has been problematic because of the experimental difficulty in isolating rat embryonic stem cells, needed to generate targeted genetic mutants with which scientists can discern specific gene function. Resource centers are needed to serve as centralized stock centers and information centers on rat models of disease. The centers will focus on production of genetically engineered animals and assessment of the resulting phenotypes. Separately, better cryopreservation techniques are to be developed to preserve gametes.

Bioengineering, Bioimaging, and Bioinformatics

Instrumentation Exceeding $0.5 Million. Most advances in biomedical research today depend increasingly on advanced instrumentation that often costs in excess of $0.5 million. Currently there is no NIH-wide program to systematically address needs in this cost range. Therefore, NCRR plans to provide support to acquire high-end instrumentation (>$0.5M), including very high-field NMR spectrometers, synchrotron macromolecular structure facilities, high-resolution mass spectrometers, cryoelectron microscopes, as well as high-performance supercomputers, to a broad community of basic and clinical scientists. Approximately $10 million has been requested for this new activity.

Increase Integrated and Shared Instrumentation Core Funding. The NCRR plans to expand the existing Shared Instrumentation Grant program to meet the needs of basic and clinical investigators who, in the post genome sequencing era, are becoming critically reliant on new high-throughput, highly sensitive, expensive research instruments in the $100,000 to $500,000 cost range. NCRR encourages recipient institutions to establish centralized, integrated core instrument facilities to offer NIH-supported investigators access to new technologies and

technical expertise. An increase of approximately $2.7 million has been requested for this activity.

Establish Distributed Network Infrastructure. The NCRR plans to establish a high-speed, web-based network for the storage, retrieval, fusion and analysis of neuromedical images with additional capability for access to existing proteomics and genomic databases. A testbed will be created with seven Biomedical Technology (BT) Centers, all co-located with General Clinical Research Centers. This Biomedical Imaging Research Network (BIRN) will be developed in concert with the University of California at San Diego and the National Science Foundation, and will serve as a test bed for neuroimaging research. The goal is to subsequently expand the network to facilitate all appropriate biomedical research across NCRR-supported GCRCs, BT and other resource centers, and also to accommodate investigators who currently do not have ready access to NCRR resource centers through wireless technology.

New Preventive Strategies Against Disease

Establish Islet Cell Resource Centers. A recent study reported that patients with Type I diabetes who received human islet cell transplants could attain long-term independence from insulin injections. To extend and reproduce these observations, the National Center for Research Resources (NCRR) will establish up to six Islet Cell Resource Centers (ICRCs) for the isolation, purification, characterization, and transplantation of human pancreatic islet cells. Since pancreatic tissue availability is limited, the ICRCs will also optimize islet cells harvested from pancreatic tissue and optimize conditions for maintaining peak islet cell function for a prolonged duration. This effort is to be jointly supported with the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International.

An Administrative and Bioinformatics Coordinating Center (ABCC) will coordinate activities for this consortium, organize its meetings, and correlate data that reflect the efficacy of both the methods used to prepare islets and the assays that predict functionality and clinical outcome. The ABCC, independent of the ICRCs, will manage data for all clinical protocols, including patient accrual, demographics, and baseline assessments, as well as the relevant laboratory and clinical data.

Health Disparities

Establish a Web-based Clinical Trials Network for Minority Serving Institutions (MSI). NCRR will establish a web-based clinical trials network for minority serving medical schools, similar to the web-based Cystic Fibrosis (CF) Network for Phase I and II clinical trials for participating General Clinical Research Centers. This network will facilitate the minority-serving institutions' participation in NIH-supported multi-site clinical trials as well as other research studies. The MSI network will concentrate on those trials which address diseases that disproportionately affect minority and underserved populations.

Establish Comprehensive Centers for Health Disparities (CCHD) Research. The CCHDs will develop the RCMI medical schools' capacities to conduct basic and clinical research in diabetes (Type II) and cardiovascular disease, both of which disproportionately affect

minority populations. The CCHDs will provide support to further develop the requisite research infrastructure, recruit magnet clinical investigators, recruit and develop promising junior faculty, and facilitate substantial collaboration between the RCMI grantee institutions and more research-intensive universities.

Research Training and Career Development

Initiate Veterinary Student Clinical Research Program. A 1-year veterinary student mentored research training program, usually between the third and fourth years of veterinary school, will be initiated to encourage qualified students to pursue careers in laboratory animal-oriented research by providing hands-on research opportunities in a mentored setting. This program is intended to begin to address the marked shortage of research-trained veterinarians in biomedical research.

Enhance Clinical Research Career Development Opportunities. To foster and maintain interest in clinical research, NCRR will enhance its support for clinical research career development opportunities. Through the GCRC program, NCRR will continue to support progressively more K23s. In addition, NCRR will modify the Clinical Research Scholars program that provides didactic training for one to three years and may lead to a M.S. or M.P.H. degree. The Mentored Medical or Dental Student program provides support for one year of didactic clinical investigation and mentored research experience at institutions with a GCRC. Fundamental concepts of clinical research, bioethics, biostatistics, and applications of research technologies to patient oriented research may be included in a curriculum specifically designed for the student. In addition, NCRR will participate in the loan repayment program for NCRR-supported outstanding junior investigators who are pursuing a patient-oriented clinical research career.

A new program will provide support for pilot studies for promising investigators who choose to pursue careers in patient-oriented research. Applications are to be reviewed through a local institutional GCRC review committee. Awards are intended to enable promising junior faculty to have protected time to conduct preliminary research studies to test hypotheses or generate "a proof of principle" that relate to studies of human disease mechanisms, prevention, and therapeutic strategies. The preliminary data are to be included in competitive grant applications to NIH or other appropriate funding agencies.

Enhance Minority Clinical Research Career Development. More well trained minority clinical investigators are needed to effectively address health disparities in minority populations. Many investigators associated with minority medical schools have not had the opportunity to take formal course work directly relevant for clinical research. A Minority Clinical Research Scholars program will provide mentored clinical research experience and didactic training that is to be designed specifically for the Scholar. Instruction will include fundamental concepts of clinical research, applications of technologies and their analyses, as well as bioethics, study design, bioinformatics, grantsmanship, and the responsible conduct of clinical research.

Research Capacity

Support Biomedical Research Facilities Construction. Funds to address the need for biomedical research facilities will be provided through the NCRR Research Facilities Improvement Program (RFIP). These funds are awarded competitively based on several factors, including efficient use of space for NIH-supported biomedical research, impact of space on health-related research in the future, and condition and utilization of existing research facilities. The grants have an impact well beyond the funds awarded since they often facilitate new research activities and improve research efficiency and capacity. In addition, the NIH awards serve to facilitate the institution's considerable leveraging of funds from donors by as much as 20-fold in some cases.

Construct and Improve Chimpanzee Facilities. Chimpanzees originally bred for AIDS research have thus far not been useful models for studies of AIDS-virus pathogenesis. Although chimpanzees are still critical for studies of respiratory syncytial virus, hepatitis, malaria, and potentially for AIDS vaccine and gene transfer studies, they are used in relatively small numbers. Thus, in concert with the National Academy of Sciences, a plan was devised to consolidate the animals supported by NIH in a more cost-effective configuration. To do this, there is a need to renovate and construct appropriate animal housing to assure the well-being and safety of these research animals and the individuals who work with them. Finally, a new bill (P.L. 106-551) authorizes support of a sanctuary system to host chimpanzees no longer needed for biomedical research. This effort will require construction of the facilities at a sanctuary along with providing the costs to maintain the animals.

Upgrade Animal Facilities for Biomedical Research. NCRR's Animal Facilities Improvement Program (AFIP) is critical to helping research institutions upgrade their animal research facilities to accommodate sophisticated research with genetically altered animal models. Support for those institutions needs to be increased to be responsive to their collective expanding needs. Separately, minority-serving (MS) graduate and health professions schools have an urgent need to upgrade their animal research facilities. To address that specific need, NCRR has developed a special program for MS-institutions; the activity will provide competitive support to upgrade their facilities to meet acceptable standards for research and to be eligible for accreditation through the Association for Assessment and Accreditation of Laboratory Animal Care International.

Enhance the Biomedical Research Capacities of Institutions within the IDeA States. The NIH Institutional Development Award program provides support to build the biomedical research capacities of institutions which have not previously fully participated in biomedical research. A cohort of 23 States and the Commonwealth of Puerto Rico was selected for this program based on their level of NIH research grant funding and success rates for NIH grant awards over the past 5 years. That cohort traditionally has received only five percent of total NIH funds awarded annually. In response to this need, NIH has developed two programs—Centers of Biomedical Research Excellence (COBRE) and Biomedical Research Infrastructure Networks (BRIN)—to enhance the biomedical research capacities among the institutions in the 23 eligible states and Puerto Rico. The COBRE program provides flexible support to augment and strengthen the institutional biomedical research infrastructure by

providing support for laboratory renovations, research equipment and development of competitive biomedical research faculty. COBRE supports a multidisciplinary team, led by an established biomedical scientist, to increase the faculty pool which will become competitive for NIH grants.

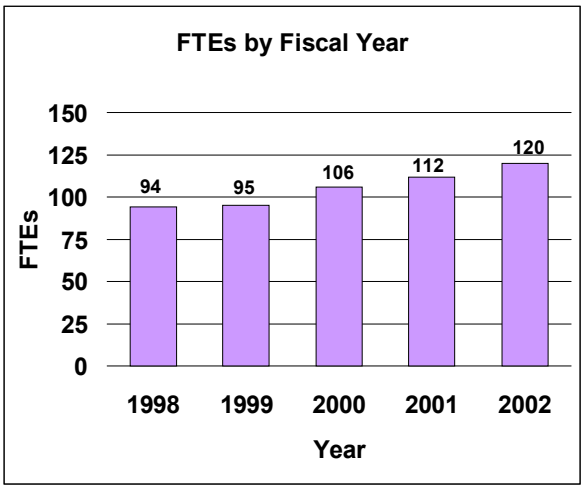
In contrast, the BRIN program enhances the educational infrastructure and research capacities of institutions. BRIN requires activities, starting at the community college or baccalaureate level, to enhance the quality of the undergraduate science faculty of participating institutions in order to improve the quality of science majors in the undergraduate institutions. BRIN program support is intended to prepare outstanding students for graduate schools in their states where they may pursue biomedical research careers or, alternatively, enter the local workforce to help upgrade the technical expertise of the state's workforce which will become more attractive to the private sector and, as a consequence, may have a positive impact on the local economy. BRIN also provides support for faculty development at the graduate school level. In Fiscal Year 2002, approximately $75 million will be provided for continuing support and further development of the Biomedical Research Infrastructure Networks that were initially established in Fiscal Year 2001. In addition, those states that did not receive a BRIN award in Fiscal Year 2001 will have a special opportunity to compete for a BRIN award in Fiscal Year 2002.

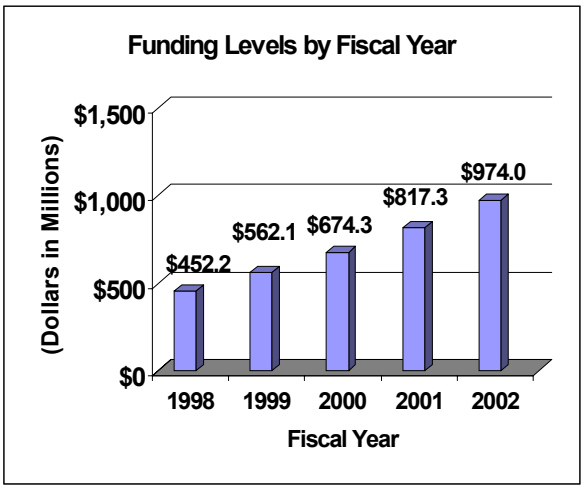
Expand Major Histocompatibility Complex Activity. This activity will expand the pool of rhesus monkeys with defined major histocompatibility complex (MHC) haplotypes, or genetic background, for studies of HIV/AIDS pathogenesis and vaccine development. Preliminary studies strongly support this approach in view of the observation that monkeys of certain MHC haplotypes have better immunologic responses to the AIDS virus. A larger pool of animals with defined MHC haplotypes is essential for facilitating the development of an effective AIDS vaccine as well as a providing an animal model to ascertain how HIV/SIV induces pathology. By using animals of a uniform haplotype, fewer animals are required and experimental variability is reduced. Animal colonies will be screened and expanded at Regional Primate Research Centers and at other research resources that will generate Specific Pathogen Free (SPF) animals of known MHC haplotype and defined SPF status.

Budget Policy

The Fiscal Year 2002 budget request for the NCRR is $974,038,000, including AIDS, an increase of $156,785,000 and 19.2 percent over the Fiscal Year 2001 level, and $299,469,000 or 44 percent over Fiscal Year 2000.

A 5 year history of FTEs and funding levels for NCRR is shown in the graphs below:





One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2002 request for NCRR reflects average cost decreases for competing RPGs estimated at 2.1 percent, reflecting the initiation of a program of smaller grants. Noncompeting RPGs will receive increases of 3 percent on average for recurring direct costs. In Fiscal Year 2002, total RPGs funded will be 229 awards, an increase of 8 awards over the Fiscal Year 2001 estimate, the highest annual total ever awarded.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the Fiscal Year 2002 request, NCRR will support 93 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over Fiscal Year 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

The Fiscal Year 2002 request includes funding for 312 research centers, 454 other research grants, including 13 new clinical career awards, and 9 R&D contracts. The R&D contracts mechanism also includes support for 15 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs.

The NCRR budget has increased at a rate greater than the overall NIH budget, almost doubling in just 3 years. Much of the NCRR's increase has been targeted to new programs, to meet the infrastructure demands of the expanding NIH portfolio. The NCRR has been diligently

recruiting staff over the past 2 years to deal with these infrastructure needs. In addition, the NCRR will increase support for travel for administrative visits to grantees and for site visits, computer equipment and furniture, supplies, computer time and other centrally supplied services. NCRR must also increase substantially the number of meetings and workshops, both scientific and technical, for the investigators and institutions who will be the recipients of NCRR grant funds, to determine resource needs of the research community over the next few years, and to begin implementation of the chimpanzee sanctuary legislation. These needs require an 11.5 percent increase in Research Management and Support.

The mechanism distribution by dollars and percent change are displayed below: